Pyrin Q148 mutation and familial Mediterranean fever

Sir,

Familial Mediterranean fever (FMF) is an auto-inflammatory disease with an autosomal recessive inheritance. Defects in the protein pyrin cause the characteristic attacks of the disease.\(^1\),\(^2\) More than 20 mutations have been identified in the gene coding pyrin. Booth et al.\(^3\) recently presented their studies in an interesting mutation, the E148Q mutation, in different populations. They have commented that individuals homozygous for the pyrin Q148 mutation have not been confirmed to suffer from clinical FMF.\(^3\) We would like to present for the first time two patients who have clinical FMF who were homozygous for the pyrin Q148 mutation.

The first patient presented with complaints of fever and severe abdominal pain. Acute-phase reactants were elevated, with an erythrocyte sedimentation rate (ESR) of 90 mm/hr, as well as elevated C-reactive protein (CRP) and fibrinogen concentrations. He had had these attacks, sometimes accompanied by arthralgia, since the age of 5 years. They occurred once or twice a month and lasted for 2 to 3 days, remitting spontaneously thereafter. Family history was negative. Serum IgD level was normal. He was started on colchicine, with a complete response and normalization of all acute-phase reactants. He was homozygous for the pyrin Q148 mutation.

The second patient presented at the age of 10 with daily peaks of fever, arthritis at the ankle, a rheumatic rash during fever and elevated ESR of 127 mm/h and a CRP elevated to 41 times the normal for the lab. He had no conjunctivitis. He was diagnosed as systemic juvenile rheumatoid arthritis (JRA), and was started on with corticosteroids and methotrexate. He had previously presented with two short attacks of fever and arthritis/arthralgia in the last 9 months. The family history was negative.

Although the typical attacks features of systemic JRA disappeared with the aforementioned treatment, his acute-phase reactants remained high. He started to have occasional attacks of fever, abdominal pain and arthralgia. He was suspected to have FMF, and was started on colchicine 19 months later. His attacks subsided and ESR returned to normal. He was homozygous for the Q148 mutation.

A number of criteria have been introduced for the clinical diagnosis of FMF. FMF may be diagnosed in a patient with short (typically 1–3 days), recurrent and self-limited attacks of fever and serositis with a marked rise in the acute-phase reactants as evidenced in these patients. Both these patients also fulfil the criteria introduced by Livneh et al.\(^4\). Their IgD levels were normal, and the attacks were not typical of either hyper IgD syndrome or TNF-receptor-associated periodic fever syndrome. The features of the attacks and dramatic response to colchicine therapy confirm the diagnosis of FMF. Since they were shown to be homozygous for the Q148 mutation, we suggest that this was a disease-causing mutation in these FMF patients.

Patients with FMF are known to have elevated acute-phase reactants such as an elevated C-reactive protein (CRP) level, even in between the attacks. Booth et al.\(^5\) have suggested that the pyrin Q148 mutation may occur in different ethnic groups, and that an enhanced inflammatory response may have conferred a survival benefit during evolution in these people. It may be suggested that the primed inflammatory milieu of the CRP pathway may predispose these patients to certain rheumatic diseases such as the systemic JRA observed in the second patient.

Future studies will illuminate whether additional genetic/environmental factors are important in the
clinical manifestation of the disease(s) in these individuals.

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References


